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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,823	06/13/2005	L Julie Huber	13407-026US1	5992

26161 7590 09/19/2007
FISH & RICHARDSON PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
LEE, JAE W	
ART UNIT	**PAPER NUMBER**
1656	
MAIL DATE	**DELIVERY MODE**
09/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,823	HUBER ET AL.	
	Examiner	Art Unit	
	Jae W. Lee, Ph.D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07/03/2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *12-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application status

Claim(s) 1-21 is/are pending in this application.

Priority

A claim of priority to applications, PCT/US03/39794, filed on 12/15/2003, and US Provisional Application No. 60/433,096, filed on 12/13/2002, is acknowledged.

Election

Applicant's election without traverse of Group I, Claims 1-11, and a species of SIRT1 in the response filed on 07/03/2007, is acknowledged.

Claim(s) 12-21 is/are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Objections to the Specification

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). To be in compliance, Applicants should identify nucleotide sequences of at least 10 nucleotides and amino acid sequences of at least 4 amino acids in the specification by a proper sequence identifier, i.e., "SEQ ID NO:" (see MPEP 2422.01). If these sequences have not been listed in the computer readable form and paper copy of the sequence listing, applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing", an initial paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d). See particularly pg. 37, line 1-4 of the specification containing a reference to "SEQ ID NO. 16" which is not disclosed in the sequence listing filed on 07/03/2007.

Appropriate correction for each error is required.

Claim Objections

Claim(s) 4 and 6-8 is/are objected to because of the following informalities:

Claim 4 is objected to because the recitation of "the cytochrome c polypeptide is human" can be improved with respect to clarity. A polypeptide cannot be human. The Examiner suggests replacing "human" with ---human cytochrome c polypeptide---.

Claims 6-8 are objected to because abbreviations such as "SIR" or "SIRT" should be written out in full when used for the first time.

Claim 8 is objected for containing non-elected subject matter, i.e., SIRT2 and SIRT3.

Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 are rejected under 35 U.S.C. § 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are directed to (1) a method of evaluating a compound, the method comprising contacting a genus of polypeptides having acetylase or deacetylase activity, or any fragment thereof, with a compound, in the presence of cytochrome c

polypeptide, and evaluating if the compound modulates interaction between the polypeptide and the cytochrome c; (2) a method comprising: contacting a genus of cells which expresses any polypeptide having acetylation or deacetylation activity and a cytochrome c polypeptide with a test compound, and determining if the test compound modulates acetylation of the cytochrome c polypeptide; and (3) a method of evaluating a test compound, the method comprising: contacting a genus of polypeptides having acetylase or deacetylase activity, or any fragment thereof, with a test compound, in the presence of a cytochrome c polypeptide, in vitro, and evaluating if the test compound modulates interaction between the polypeptide and the cytochrome c; contacting a genus of cells which expresses any polypeptide having acetylation or deacetylation activity and a cytochrome c polypeptide with the test compound, and determining if the test compound modulates acetylation of the cytochrome c polypeptide in the cell.

To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of [compositions or methods], it must be clear that: (1) the identifying characteristics of the claimed [compositions or methods] have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed.

The specification discloses only a single representative species of a genus of polypeptides, human SIRT2 and human SIRT3, i.e., SEQ ID NOs: 2 and 3 respectively, that can be used by the claimed method. However, this single disclosed species fails

to provide adequate written description for a genus of polypeptides having acetylase or deacetylase activity, or any fragment thereof, and a genus of cells which expresses any polypeptide having acetylation or deacetylation activity as encompassed by the claims, which encompasses any polypeptide having acetylase or deacetylase activity, or any fragment thereof with or without any function, and any cell including transgenic animals and plants that can be used by the claimed methods.

In this case, the specification fails to describe any identification of structural characteristics or properties of (1) any polypeptides having acetylation or deacetylation activity, (2) any fragment thereof with or without any function, and (3) any fragment thereof with or without any function, and any cell including transgenic animals and plants that can be used by the claimed methods. Taken together, the genera of "polypeptides," "fragments thereof," and "cells" encompasses widely variant species, having essentially any structure, and the disclosure lacks adequate description with respect to the interaction between said genera and the cytochrome c, which can be used by the claimed methods for evaluating compounds. Please refer to the M.P.E.P. section 2163 [R-5] under II, A, 3, (a), (ii) for more details with respect to sufficient number of representative species that should be disclosed to describe a widely variant genus.

Given the lack of additional representative species of the above-mentioned genera, as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, because the specification, while being enabling for an *in vitro* method of measuring deacetylation activity of human SIRT2 and human SIRT3 comprising the amino acid sequence as set forth in SEQ ID NOs: 2 and 3, respectively, on chemically acetylated cytochrome c polypeptides, does not reasonably provide enablement for (1) a method of evaluating a compound, the method comprising contacting any polypeptide having acetylase or deacetylase activity, or any fragment thereof, with a compound, in the presence of cytochrome c polypeptide, and evaluating if the compound modulates interaction between the polypeptide and the cytochrome c; (2) a method comprising: contacting any cell which expresses any polypeptide having acetylation or deacetylation activity and a cytochrome c polypeptide with a test compound, and determining if the test compound modulates acetylation of the cytochrome c polypeptide; and (3) a method of evaluating a test compound, the method comprising: contacting any polypeptide having acetylase or deacetylase activity, or any fragment thereof, with a test compound, in the presence of a cytochrome c polypeptide, in vitro, and evaluating if the test compound modulates interaction between the polypeptide and the cytochrome c; contacting any cell which expresses any polypeptide having acetylation or deacetylation activity and a cytochrome c polypeptide with the test

compound, and determining if the test compound modulates acetylation of the cytochrome c polypeptide in the cell as encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

Claims 1-11 are so broad as to encompass (1) a method of evaluating a compound, the method comprising contacting any polypeptide having acetylase or deacetylase activity, or any fragment thereof, with a compound, in the presence of cytochrome c polypeptide, and evaluating if the compound modulates interaction between the polypeptide and the cytochrome c; (2) a method comprising: contacting any cell which expresses any polypeptide having acetylation or deacetylation activity and a cytochrome c polypeptide with a test compound, and determining if the test compound modulates acetylation of the cytochrome c polypeptide; and (3) a method of evaluating a test compound, the method comprising: contacting any polypeptide having acetylase or deacetylase activity, or any fragment thereof, with a test compound, in the presence of a cytochrome c polypeptide, in vitro, and evaluating if the test compound modulates interaction between the polypeptide and the cytochrome c; contacting any cell which expresses any polypeptide having acetylation or deacetylation activity and a cytochrome c polypeptide with the test compound, and determining if the test compound modulates acetylation of the cytochrome c polypeptide in the cell.

The specification discloses an *in vitro* method of measuring deacetylation activity of human SIRT2 and human SIRT3 comprising the amino acid sequence as set forth in SEQ ID NOs: 2 and 3, respectively, on chemically acetylated cytochrome c polypeptides. With regard to the use of all "polypeptides having acetylase or deacetylase activity" or all "fragments thereof" in the claimed method, it is noted by the Examiner that not all structurally different polypeptides having acetylase or deacetylase activity, and any fragment thereof would be able to acetylate or deacetylate cytochrome

c polypeptides because said polypeptides or fragments thereof require functional catalytic domains which acetylate or deacetylate cytochrome c polypeptides at specific acetylation/deacetylation sites. For this reason, a method of evaluating a compound, that modulates interaction between the polypeptide and the cytochrome c via said polypeptides' acetylase or deacetylase activity on the cytochrome c polypeptide would not work if the polypeptides or any fragment thereof, optionally expressed by any cell, were mutated at the regions around the acetylase or deacetylase catalytic domains. In addition, the claimed methods would not work if the polypeptide or any fragment thereof, optionally expressed by any cell, were mutated at the regions which are required for physical interactions with the cytochrome c, or those that are required for recognizing the acetylation/deacetylation sites on cytochrome c polypeptides. Such methods would not enable one of skill in the art to evaluate or determine compounds that modulate the acetylation/deacetylation of cytochrome c polypeptides by using any polypeptide having acetylase or deacetylase activity or any fragment thereof, which may result in apoptosis when expressed by any cell. Therefore, the disclosure of an *in vitro* method of measuring deacetylation activity of human SIRT2 and human SIRT3 comprising the amino acid sequence as set forth in SEQ ID NOs: 2 and 3, respectively, on chemically acetylated cytochrome c polypeptides does not commensurate with the breadth of claimed methods encompassing the use of all possible "polypeptides having acetylase or deacetylase activity or any fragment thereof" optionally expressed in any cell.

It is noted by the Examiner that the recitation of "a cell which expresses..." in claims 9 and 11 encompasses the use of transgenic animal or plants, which is not supported or disclosed in the instant application.

The claims rejected under this section of U.S.C. 112, first paragraph, do not place any structural limits on the "polypeptide," and "fragment thereof," which are used in the claimed methods. Since the amino acid sequence of a peptide determines its structural and functional properties, predictability of which peptides can be used while obtaining the desired function requires a knowledge of and guidance with regard to which amino acids in the peptide's sequence, if any, are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the peptide's structure relates to its desired function. In addition, the scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of different peptides/proteins.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any polypeptide having acetylase or deacetylase activity or any fragment thereof used in the claimed methods because the specification does not establish: (A) structures or regions of any polypeptide having acetylase or deacetylase activity or any fragment thereof which may be modified without affecting the desired biological function of any polypeptide or any fragment, i.e., deacetylase activity; (B) adequate guidance with respect to the structure of domains required for catalysis of acetylation or deacetylation, physical interaction with cytochrome c, and/or recognizing acetylation/deacetylation site(s) of cytochrome c that could be modified or fragmented without affecting the desired biological function of any polypeptide or any fragment; (C) the general tolerance of any polypeptide having acetylase or deacetylase activity or any fragment thereof to modification and extent of such tolerance without affecting the desired biological function of the mutant or the fragment; (D) a rational and predictable scheme for modifying any amino acid residue of any polypeptide having acetylase or deacetylase activity or any fragment thereof with an expectation of obtaining the desired activity/utility; (E) adequate guidance with respect to the interaction between any polypeptide having acetylase or deacetylase activity or any fragment thereof, and the cytochrome c that can be used in the claimed methods for for the purpose of identifying compounds that can modulate cytochrome c-mediated apoptosis via changing the cytochrome c acetylation status, according to the specification pg. 33, last paragraph; and (F) the specification provides insufficient

guidance as to which of the essentially infinite possible choices is likely to be successful.

Because of this lack of guidance, and the fact that the relationship between the polypeptide sequence of a protein and its activity/function is not well understood and unpredictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to make and use the claimed methods.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any polypeptide having acetylase or deacetylase activity or any fragment thereof, optionally expressed in any cell used in the claimed methods having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Conclusion

Claims 1-11 are rejected for the reasons as stated above. Applicants must respond to the objections/rejections in this Office action to be fully responsive in prosecution.

The instant Office action is non-final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jae W. Lee whose telephone number is 571-272-9949. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Patent Examiner: Jae W. Lee, Ph.D.

RICHARD HUTSON, PH.D.
PRIMARY EXAMINER